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10/539,208	05/24/2006	David Raab	LT00379 US	2327
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EXAMINER ZHOU, SHUBO				
ART UNIT 1631		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/539,208

Applicant(s)

RAAB ET AL.

Examiner

SHUBO ZHOU

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 December 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 and 17-35 is/are pending in the application.
- 4a) Of the above claim(s) 17-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 and 31-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-940)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Amendments/Status of the Claims

Applicant's amendments filed 12/28/10 are acknowledged, but only the amendment to the claims is entered.

The amendment to the specification has not been entered as it is not complied with 37 CFR 1.121, which requires that "[a]mendments to the specification, other than the claims, computer listings (§ 1.96) and sequence listings (§ 1.825), must be made by adding, deleting or replacing a paragraph, by replacing a section, or by a substitute specification, in the manner specified in this section." In the instant case, the amendment filed on 12/28/10 amends appears to amend sentence within a paragraph. Furthermore, no paragraph numbering is given to the specification filed on 6/17/05, which is the only specification present in the application to date, and thus it is unclear what particular paragraphs are meant by the paragraph numbers referred to in the amendment filed on 12/28/10.

Claim 16 has been canceled.

Claims 1-15, and 17-35 are pending.

Claims 17-30 have been previously withdrawn, and remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-15 and 31-35 are under examination.

Sequence Rules Compliance

Applicant pointed out that amendment to the specification filed on 5/24/06 has amended the specification to include SEQ ID NOs for the sequences on pages 41, 43, 46, 53, etc. of the specification. The sequence rules are satisfied.

Specification

The specification is objected to because of the following including informalities:

This objection is reiterated from the previous Office action because the amendment filed on 12/28/10, which is intended to overcome the objection, has not been entered for reasons set forth above.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.

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- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

In the instant case, there are no section headings for any section in the specification.

Trademarks are used in this application, such as GENBANKTM on page 56. All trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort should be made to prevent their use in any manner that might adversely affect their validity as trademarks.

The disclosure is objected to also because it contains an embedded hyperlink and/or other form or browser-executable code. Such code is present in the specification at least on pages 53, 56. Applicants are required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP ' 608.01.

Claim Rejections - 35 USC § 101

The rejection of claims 1-10 and 14-15 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the amendment filed on 12/28/10, and in light of the Interview conducted on 12/8/10 (see Interview Summary mailed on 12/15/10).

Claim Rejections - 35 USC § 112

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 31-35 are rejected under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a step of “generating, using a suitably programmed computer, a first test sequence ...” and thereafter recites step of “specifying,” another step of “generating,” a step of “assessing,” and a second step of “specifying,” where in all the steps following the first “generating,” the phrase “using a suitably programmed computer” is recited. It is thus unclear as to whether the “suitably programmed computer” recited in all the steps after the first “generating” step are the same computer as that recited in the first “generating” step and thus the computers are programmed the same way, or they can be different computers and programmed differently, but also “suitably” programmed.

Independent claim 31 is also rejected for reciting the same indefinite limitation.

All claims dependent from claims 1 and 31 are rejected for also containing the indefinite limitation.

Clarification of the metes and bounds of the claims is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 and 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoover et al. (IDS document filed 12/12/07, *Nucleic Acids Research*, 2002, Vol. 30, No. 10 e43).

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For the record, a search of the website of Nucleic Acids Research (NAR) reveals that Hoover et al. was published in May 2002. See attached copy of NAR's web pages (printed from <http://nar.oxfordjournals.org/archive/2002.dtl> on 6/21/10).

This rejection is reiterated from the previous Office action. Applicant's arguments filed on 12/28/10 has been fully considered and responded below.

The instant claims are drawn to a method for optimizing a nucleotide sequence for the expression of a protein on the basis of the amino acid sequence of the protein, which comprises the following steps (step numbers were added by the examiner for convenience):

- 1) generation of a first test sequence of n codons which correspond to n consecutive amino acids in the protein sequence, where n is a natural number and is less than or equal to N , the number of amino acids in the protein sequence;
- 2) specification of m optimization positions in the test sequence which correspond to the position of m codons at which the occupation by a codon, relative to the test sequence, is to be optimized, where m is smaller than or equal to n and $m < N$;
- 3) generation of one or more further test sequences from the first test sequence by replacing at one or more of the m optimization positions a codon of the first test sequence by another codon which expresses the same amino acid;
- 4) assessment of each of the test sequences with a quality function and ascertaining the test sequence which is optimal in relation to the quality function;
- 5) specification of p codons of the optimal test sequence which are located at one of the m optimization positions, as result codons which form the codons of the

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optimized nucleotide sequence at the positions which corresponds to the position of said p codons in the test sequence, where p is a natural number and p is smaller than or equal to m iteration of the preceding steps, where in each iteration step the test sequence comprises the appropriate result codon at the positions which correspond to positions of specified result codons in the optimized nucleotide sequence, and the optimization positions are different from positions of result codons.

Hoover et al. disclose a method and system for automated designing oligonucleotides based on the amino acid sequence of a protein/peptide. The method includes optimizing the nucleotide sequences based on codon usage, melting temperature, etc. See at least the Abstract. The method includes reverse translate the inputted protein sequence into a first test sequence comprising codons which correspond to the consecutive amino acids in the protein sequence, where the number of codons is equal to the number of amino acids in the protein sequence. See page 2 of 7 and Fig. 1. This reads on step 1) of the instant claim 1. While Hoover et al. do not use any symbols to represent the number of codons, it would be readily apparent to one skilled in the art that any character or symbol could be used for such a purpose. For the sake of convenience for discussion in this Office action, n is used for the number of codons, and N for the number of amino acids in the test sequence. This test sequence is then broken into odd number of contiguous sections of smaller test sequences, each with a plurality of specified codons at positions corresponding to the positions of the amino acids of the test sequence for optimization. Hoover et al. disclose that stochastic optimization is used, and codons of the sections are swapped with other codons. Hoover et al. stress that during each

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optimization step, the number of mutations as well as changes in sizes diminish as the optimization process progresses. Hoover et al. also disclose that quality functions are used to assess the quality the test sequence and sections thereof including calculating scores based on codon frequency, hairpin formation and deviations from the desired melting temperature (involving GC content) and size, etc., and at the end of each optimization step, the score is recalculated for each section. When no further improvements of the scores, the sequences are optimized, and each an optimized codon is specified for each position. See Fig. 1 and page 3 of 7. This reads on steps 2)-5) of the instant claim 1. Again, it would be readily apparent to one skilled in the art that any character or symbol could be used for representing the number of codons in each section. For the sake of convenience for discussion in this Office action, m is used for the number of codons in each section. Clearly, m is small than n or N above as m represents sections of N .

Again, while Hoover et al. do not use particular characters, e.g. n , N , m , etc. to represent the number of codons, amino acids, etc., it would have been obvious to one of ordinary skill in the art at the time of the invention that any characters or symbols would have been used and sufficient for representations. Furthermore, since these characters would be used for representing the number of amino acids, codons, etc., in the test sequence or sections thereof, it would be obvious that they are natural numbers.

Hoover et al. also disclose a device, system and computer program for the method. See pages 3 of 7 and 4 of 7.

In the arguments filed 12/28/10, applicant first described Hoover's invention and the presently claimed invention on pages 16-19 and then summarized the apparent

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differences between the two on page 19. One of applicant's major argument is that in the present invention, optimization positions are specified, i.e. in every iteration, the sequence is mutated only at the specified optimization positions, which are a subset of the codons to be optimized, no at random codons and at randomly selected positions of the entire sequence as in Hoover. See page 19. This is unpersuasive. In the present invention, the specified positions to be optimized is m , but m could be equal to n , which is the number of codons, and the latter could be equal to N , which is the number of amino acids in the entire protein sequence. See claim 1. Thus, the specified codons to be optimized could include all codons of the entire sequence. Applicant also argues that in Hoover's algorithm, in every iteration the sequence is either maintained as a whole or rejected as a whole, but never maintained in part as in the present invention. This is also not persuasive because the sequence maintained in part is not a limitation in the instant claims. Applicant further argues that Hoover discloses a global optimization while the present invention is directed to a more localized optimization. This is again unpersuasive as set forth above, in the present invention, the specified positions to be optimized is m , but m could be equal to n , which is the number of codons, and the latter could be equal to N , which is the number of amino acids in the entire protein sequence. The present invention thus could also be a global optimization.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP §

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706.07(a).

Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136 (a). A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136 (a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than six months from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 9 A.M. to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran, can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Shubo (Joe) Zhou/

PRIMARY EXAMINER

